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Adalimumab for the Prevention of Uveitic Flare in Patients with Inactive Non-infectious Uveitis Requiring Corticosteroids: A Multicenter, Double-masked, Placebo-Controlled Phase 3, Randomised Controlled Trial

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Summary

Background: Non-infectious uveitis represents a potentially sight-threatening ocular disorder as a result of chronic inflammation and its complications. Therapeutic success is limited by systemic adverse effects associated with long-term corticosteroid and immunomodulator use if topical medication is not sufficient to control the inflammation. This study assessed the efficacy and safety of adalimumab in systemic corticosteroid-dependent patients with inactive, non-infectious intermediate, posterior, or panuveitis.

Methods: VISUAL II, a multinational, double-masked, phase 3 trial enrolled adult patients with inactive, non-infectious intermediate, posterior, or panuveitis requiring 10-35mg of prednisone daily to maintain inactivity. Patients were randomized 1:1 to receive adalimumab (loading dose, 80mg; biweekly dose, 40mg) or placebo and were subjected to a mandatory prednisone taper from week 2. The primary efficacy endpoint time to treatment failure (TF) a multi-component endpoint, encompassing new active inflammatory chorioretinal and/or inflammatory retinal vascular lesions, anterior chamber cell grade, vitreous haze grade and visual acuity, as well as nine ranked secondary efficacy endpoints were assessed in the intent-to-treat population. Adverse event (AEs) rates were monitored. ClinicalTrials.gov, number-NCT01124838.

Findings: 229 patients from 21 countries involving 62 study sites were enrolled. Patients receiving adalimumab were significantly less likely to have TF (hazard ratio=0·57; 95% CI, 0·39-0·84; *P*=0·004). The 40th percentile for time to TF was 4·8 months for placebo and 10·2 months for adalimumab group, respectively. Neither group reported opportunistic infections (excluding TB). No malignancies were reported in the placebo group while 1 (0.9%) adalimumab-treated patient reported non-serious squamous cell carcinoma of skin. The most

common AEs were arthralgia (Placebo: 12 [10·5%]; Adalimumab: 27 [23·5%), nasopharyngitis (Placebo: 16 [16·7%]; Adalimumab: 8 [15·7%], and headache (Placebo: 17 [14·9%]; Adalimumab: 17 [14·8%]).

Interpretation: In systemic corticosteroid-dependent patients with inactive, non-infectious intermediate, posterior, or panuveitis adalimumab significantly lowered the risk for uveitic flare or visual acuity loss upon corticosteroid withdrawal. Based on the limited safety data, no new safety signals were observed. The rate of AEs was similar with adalimumab compared with placebo, although it is recognized that the study sample size does not allow complete conclusions on the safety of the therapy.

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Introduction

Uveitis and its associated complications account for approximately 10-15% of preventable blindness in western countries.[1-3] Corticosteroids (CS) have been the mainstay of uveitis treatment, but ocular and/or systemic adverse effects limit their long-term use in the treatment of intermediate, posterior, or panuveitis.[4-6] The guidance from the Standardization of Uveitis Nomenclature (SUN) working group supports the use of systemic CS-sparing agents in patients on chronic CS treatment with quiescent disease; the ability to achieve a reduction in CS dose below a clinically meaningful threshold while maintaining inactive disease is a key determinant of treatment success.[6]

There are few currently approved non-CS immunomodulatory agents for uveitis worldwide that can provide long-term control of uveitis[7,8]. Globally, there is an unmet need that warrants pursuit of additional effective therapies in steroid-dependent patients with non-infectious uveitis who are at risk for long-term CS side effects.

Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine produced by various cells including macrophages and neutrophils.[9-12] Adalimumab (Humira®; AbbVie Inc., North Chicago, IL) is a recombinant human immunoglobulin (IgG1) monoclonal antibody that binds specifically to TNF and neutralizes its biological function.[13] Adalimumab's safety and efficacy profile spans over 13 years for various approved inflammatory conditions such as rheumatoid arthritis, psoriasis, ankylosing spondylitis (AS), Crohn's disease, ulcerative colitis, hidradenitis suppurativa and juvenile idiopathic arthritis (JIA).[13] Several prospective studies, including the VISUAL I clinical trial, have shown the efficacy and safety of anti-TNF agents (infliximab and adalimumab) in the treatment of chronic and refractory uveitis and in reducing CS use. [14-19]

There are two major therapeutic goals in uveitis: (1) To achieve quiescence in an eye with active intraocular inflammation, which was the focus of the VISUAL I trial. (2) To prevent a recurrence of intraocular inflammation, and reduce side effects of long-term CS usage in patients with a history of uveitic flare controlled by oral CS (≥10mg/d) treatment. The VISUAL II study was a randomized, double-masked, placebo-controlled clinical trial designed to assess the efficacy and safety of adalimumab in preventing reactivation of non-infectious intermediate, posterior, and panuveitis dependent on CS to maintain inactivity.

Methods

Study design and oversight

VISUAL II was a phase 3, randomized, double-masked, placebo-controlled study conducted in 21 countries involving 62 study sites between August 2010 and May 2015. The study protocol was approved by the responsible ethics committees and internal review boards and was performed in compliance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and applicable local regulations.

Study participants

Eligible patients included individuals aged ≥18 years with inactive non-infectious intermediate, posterior, or panuveitis. Key inclusion criteria were inactive disease ≥28 days prior to the baseline visit and daily oral prednisone ≥10 to ≤35mg to maintain inactive uveitis. Inactive uveitis was defined as eyes without active inflammatory chorioretinal and/or retinal vascular lesions, anterior chamber (AC) cell grade ≤0·5+ (SUN, Working Group criteria; score range, 0–4+),[20] and/or vitreous haze (VH) grade ≤0·5+ (National Eye Institute [NEI] criteria adapted by SUN).[20,21] To demonstrate CS dependency, the patient should have a documented history of

experiencing at least 1 disease flare within 18 months of the screening visit. Additionally, this flare should have occurred during or up to a maximum of 28 days after tapering off the oral corticosteroid therapy.Patients were allowed only one ongoing immunosuppressive therapy (not including corticosteroids) within the last 28 days prior to the baseline visit. Additionally, the dose of the 1 concomitant immunosuppressive therapy allowed had to be stable for at least 28 days prior to baseline and within the dose range as mentioned in Appendix, Table S1. Patient with corneal or lens opacity that precluded visualization of the fundus or that likely required cataract surgery during the duration of the trial were excluded. Patients with isolated anterior or infectious uveitis or any condition precluding safe participation in the study or interfering with study assessments were excluded (see appendix p.4 for complete inclusion and exclusion criteria).

Randomisation and Masking

At the baseline visit, patients were randomised to adalimumab or placebo treatment groups in a 1:1 ratio stratified by baseline immunosuppressant treatment with an interactive voice/web response system that assigned allocation numbers and treatments. Randomization was performed using a block size of 4. This was a double-masked study. All sponsor personnel with direct oversight of the conduct and management of the study (with the exception of those providing study treatments), investigators, study site personnel, and patients were masked to treatment. Masking was maintained throughout the 80-week treatment period.

Procedures

According to the treatment regimen, adalimumab and placebo were supplied in pre-filled syringes and were administered subcutaneously. The adalimumab group received an 80-mg baseline loading dose followed by 40-mg doses every other week starting at week 1 for the

duration of the study. Patients were on 10 to 35mg/d of oral prednisone at Baseline and from week 2, all patients underwent a mandatory prednisone taper to 0-mg by week 19. The schedule of study procedures is described (see appendix p.11). Presence or absence of inflammatory chorioretinal and/or retinal vascular lesions was determined by dilated indirect ophthalmoscopy. AC cell counts and cataracts were assessed using slit-lamp biomicroscopy at every study visit. The AC cell counts were graded according to SUN criteria while the cataracts were graded using Age-Related Eye Disease Study (AREDS) lens opacity grading system.[20,22] VH was assessed using dilated indirect ophthalmoscopy and graded using SUN-adapted NEI criteria.[20,21] ME was assessed using OCT (Stratus OCT [Carl Zeiss Meditec, Inc., Jena, Germany], Cirrus HD-OCT [Carl Zeiss Meditec, Inc.], or Spectralis [Heidelberg Engineering, Heidelberg, Germany]) (see appendix p.2).

Outcomes

Clinic visits were scheduled at screening; baseline; week 2, 4, and approximately every 4 weeks thereafter. Patients were assessed until treatment failure was determined or until completion of 80 weeks of double-blind masked treatment. The maximum duration of treatment was 80 weeks or when the 106th treatment failure occurred.

Beginning at or after week 2 and at every subsequent visit thereafter, treatment failure was determined if any of the following criteria were met in at least 1 eye: new active, inflammatory chorioretinal and/or inflammatory retinal vascular lesions (as determined by the investigator using clinical examination and/or ancillary testing such as fluorescein angiography); worsening of BCVA by ≥15 letters; 2-step increase in AC cell grade; 2-step increase in VH grade relative to Baseline.

The primary efficacy endpoint was time to treatment failure. Nine ranked secondary endpoints were tested in hierarchical order for statistical significance between adalimumab and placebo groups: (1) change in AC cell grade in each eye; (2) change in VH grade in each eye; (3) change in BCVA (logMAR) in each eye; (4) time to optical coherence tomography (OCT) evidence of macular edema (ME) in at least 1 eye; (5) percent change in central retinal thickness (CRT, i.e. CRT as defined by center point thickness for this analysis) in each eye; (6) change in NEI Visual Functioning Questionnaire-25 (VFQ-25) composite score; (7) change in VFQ-25 distance vision subscore; (8) change in VFQ-25 near vision subscore; and (9) change in VFQ-25 ocular pain subscore. All ranked secondary endpoints were analyzed comparing baseline with the final or early termination visit, except for endpoint 4.

Adverse events (AEs) were monitored throughout the study and reported from the first dose of study drug until 70 days after the last dose of study drug or until patients were rolled into a separate extension study. Serious AEs were collected from the time of informed consent. AEs were tabulated using Medical Dictionary for Regulatory Activities (MedDRA) version 17·0 system organ class and preferred terms. Adalimumab immunogenicity was evaluated at multiple time points throughout the study.

Statistical analysis

Sample size determination

An overall treatment failure rate of 30% – 35% at 6 months is assumed with an expected treatment effect corresponding to an absolute difference of 15% between the treatment failure rates in the adalimumab and placebo group. A conservative assumption was that treatment failures would begin to occur after 2 months because of prednisone taper. A pooled dropout rate of 35% over 12 months was also assumed. Based on these assumptions, 84 to 107 treatment

failures were sufficient for a 2-sided significance level of 5% using a log-rank test. This calculation assumed power of 80% and an average accrual rate of 3 patients per month in the first 28 months and 16 patients per month thereafter.

A series of calculations with different sample sizes using the event rate, recruitment rate, and dropout rate assumptions described above was performed using East5, v5·2·0·0 (Cytel Inc., Cambridge, MA). To achieve approximately 96 treatment failure events, it was determined that a sample size of approximately 220 patients was needed.

An Independent data monitoring committee (IDMC) was set up at the beginning of the trial. The IDMC independently monitored and assessed data and was in effect until the end of the study. At each committee meeting, the IDMC undertook a comprehensive review and assessment of the cumulative safety data. The IDMC met approximately every 6 months or at a frequency determined by the IDMC to render their recommendation for either the termination or continuation of the study or an amendment to the study. The IDMC analyses were conducted by a statistics vendor (Axio Research, LLC, Seattle, USA) external to AbbVie in order for AbbVie to remain masked to the results of the study. The IDMC met 8 times and did not identify safety issues requiring either a temporary hold or an early termination of the study.

Protocol deviations were monitored via evaluation of inclusion/exclusion criteria at study entry and throughout the study. A total of 54 patients (23.9%) had important reportable deviations, including criteria violations, received excluded concomitant treatment, received wrong treatment or incorrect dose (adalimumab/placebo), received wrong treatment or incorrect dose (prednisone), and developed withdrawal criteria but was not withdrawn. No patients received a treatment to which they were not randomised for an entire period; therefore, all patients were

analyzed as randomised for both safety and efficacy analyses. Baseline characteristics were summarized using descriptive statistics.

Efficacy endpoints were analyzed in the intent-to-treat (ITT) data set (all patients randomized to treatment excluding 3 patients from 2 non-compliant sites). The primary endpoint "time to treatment failure" was compared between treatment groups using a log-rank test. A proportional hazards model with treatment as a factor was fitted to estimate the hazard ratio (HR) with its 95% confidence interval. As additional exploratory endpoints, time to treatment failure due to each component of the primary endpoint was analyzed similarly.

Testing of ranked secondary endpoints was conducted in hierarchical order and nominal *P* values for between-group differences were provided. Changes in AC cell grade, VH grade, BCVA, and CRT were compared between groups by analysis of variance with treatment as a factor adjusted for clustered observations within a patient, i.e. a repeated measures ANOVA was used to account for correlation between measurements from both eyes of a patient. CRT analysis used the OCT machine type as an additional factor. Time to OCT evidence of ME on or after week 2 was compared between groups with a log-rank test excluding patients with pre-existing ME at baseline. Changes in VFQ-25 composite score and sub-scores were compared between groups by analysis of variance with treatment as a factor. For analysis of secondary variables, with the exception of time to OCT evidence of ME, missing data were imputed using last observation carried forward.

Safety analysis was performed on the safety set which included patients who received at least one dose of adalimumab. Treatment-emergent AEs were summarized descriptively by treatment group. AEs were presented as events per 100 patient-years (100PY) to avoid confounding by between-group differences in duration of exposure to study treatment. All statistical tests were 2-

sided at a significance level of 0·05; analyses were performed by the study sponsor using SAS software (SAS Institute Inc., Cary, NC). This trial is registered with ClinicalTrials.gov, number NCT01124838.

Role of Funding Source

AbbVie funded the study, contributed to design, participated in the collection, analysis, and interpretation of the data, and in preparation and approval of this report. All authors had access to study data, reviewed and approved the final report, and take full responsibility for the accuracy of the data and statistical analysis. The corresponding author had full access to study data and had final responsibility for the decision to submit for publication.

Results

Patients

The trial recruited 229 patients between August 10, 2010 and May 14, 2015; of these 229 patients randomised to treatment, 226 were included in the ITT analyses (3 patients were excluded from 2 non-compliant sites) (placebo, n=111; adalimumab, n=115) (Figure 1). More patients were female (61%) and white (84%); 46% were diagnosed with panuveitis. Mean patient age was 42·5 years, and mean duration of uveitis was 61 months. There were no significant differences between randomised groups in demographics and baseline characteristics **(Table 1)**. Fourteen patients receiving adalimumab and 16 patients receiving placebo discontinued the study. AEs were the most common cause of discontinuation in both groups (Figure 1). The median time of follow-up, measured as duration of treatment with study drug, for placebo and adalimumab groups was 155 and 245 days, respectively.

Efficacy

An early and sustained separation of the treatment failure curves was observed between adalimumab and placebo groups. The 40th percentile for time to TF was 4·8 months for placebo and 10·2 months for adalimumab group, respectively, while median time to treatment failure was 8·3 months for placebo and not estimable (>18 months) for adalimumab, as more than half of the adalimumab-treated patients did not experience treatment failure. The risk of treatment failure for patients in the adalimumab group was significantly reduced by 43% compared to patients in the placebo group (HR, 0·57; 95% CI, 0·39–0·84; *P*=0·004), **(Figure 2A)**. Adalimumab treated patients had lower risk to fail and fewer criteria of treatment failure were met (Figure 3A).

Nine ranked secondary variables were tested in hierarchical order for statistical significance between the adalimumab and placebo groups. Overall, the hierarchical testing procedure stopped after testing the first ranked secondary endpoint as no statistically significant difference was observed between the treatment groups; p-values provided for ranked secondary endpoints are exploratory in nature. Results were numerically in favor of adalimumab for all ranked secondary variables except change from baseline in VFQ-25 near vision subscore (Table 2).

Exploratory analyses of the 4 pre-specified reasons for treatment failure were performed. The percentage of patients with treatment failure due to visual acuity showed the largest difference between the placebo and adalimumab groups (20·7% and 8·7%, respectively; Figure 3B). The risk of treatment failure based on visual acuity was reduced by 67% for patients in the adalimumab group compared to the placebo group (HR, 0·33; 95% CI, 0·16–0·70; *P*=0·002). The rates of treatment failure based on new active inflammatory chorioretinal and/or inflammatory retinal vascular lesions (HR, 0·55; 95% CI, 0·26–1·15; *P*=0·105), increase in AC cell grade (HR, 0·70; 95% CI, 0·42–1·18; *P*=0·180) and increase in VH grade (HR, 0·79; 95%

CI, 0·34–1·81; *P*=0·589; **Figure 2B)** were numerically lower in the adalimumab group compared with placebo.

Safety

The incidence of AEs was comparable between treatment groups (905 E/100PY and 879 E/100PY placebo and adalimumab, respectively (Table 3). Serious AEs were reported at rates of 14·1 E/100PY in the placebo group and 13·8 E/100PY in the adalimumab group. The most frequently reported AEs were injection site reactions (placebo, 22·6 E/100PY; adalimumab, 38·1 E/100PY) and allergic reactions (placebo, 11·3 E/100PY; adalimumab, 5·3E/100PY). Serious infections occurred at a similar rate between groups. One malignancy (non-serious squamous cell carcinoma of skin) in the adalimumab group and 1 and 3 events of latent tuberculosis were reported in the placebo and adalimumab group, respectively. No active tuberculosis, lupus or lupus-like reaction or demyelinating disorders were reported.

Seven patients (6·1%) in the placebo group and 10 patients (8·7%) in the adalimumab group discontinued study drug due to AEs. AEs leading to patient discontinuation in the adalimumab group included mycobacterium TB complex test positive (4 patients), pulmonary sarcoidosis (2 patients), and bronchitis, neutropenia, hepatic stenosis, dermatitis, and worsened migraine (1 patient each). Sixty patients were pseudophakic at baseline. Six (5.3%) patients in the placebo and 2 (1.7%) in the adalimumab groups, developed cataracts during the study. Overall, 2 patients in the placebo and 1 patient in the adalimumab group had cataract surgery/YAG-laser capsulotomy during the study, but continued in the study. AE results were consistent with the known safety profile of adalimumab across approved indications. One death due to aortic dissection and cardiac tamponade was reported post-treatment (Day 54 [18 days after last dose])

in a patient randomised to adalimumab; the investigator considered the events not related to study drug (Table 3). Six patients (5·2%, n=6/115) had anti-adalimumab antibodies (AAA^+) during the study. Five/six AAA^+ patients experienced treatment failure at 13, 16, 16, 24 and 31 weeks, respectively; median time to treatment failure was not estimable for AAA^- patients, as more than half of the AAA^- patients did not experience treatment failure (n=109).

Discussion

In the VISUAL II study, treatment of patients with inactive, non-infectious intermediate, posterior, or panuveitis with adalimumab significantly reduced the risk of treatment failure (uveitic flare or visual acuity loss), as demonstrated by an early and sustained separation of adalimumab and placebo treatment failure curves. Median time to treatment failure for adalimumab-treated patients, although not estimable, was significantly longer than placebo. Patients receiving adalimumab met fewer treatment failure criteria as compared with the placebo group. The risk of treatment failure based on logMAR BCVA (visual acuity) was reduced by 67% for patients in the adalimumab group compared to the placebo group. The rates of treatment failure based on active inflammatory lesions, AC cell grade and VH grade were numerically lower in the adalimumab group compared with placebo.

Most of the measurable effect of adalimumab was on the BCVA component of the primary efficacy endpoint. Although the effect of adalimumab on the other inflammatory components of the primary endpoint was not significant, the improvement in BCVA is likely to be through its effect on multiple aspects of inflammation within the eye, some of which may not have been included in the multiple-component endpoint. The inflammatory manifestations observed in patients with vision loss that may have been, at least in part, the cause of the vision loss were increase in AC cell and VH grade (≥1), new inflammatory/chorioretinal vascular lesions, retinal

thickening, and cataracts. The cross-sectional study by Dick et al, based on population insurance data provides supportive evidence that the presence of chronic low grade inflammation in this group is associated with worse visual outcomes.[2]

The efficacy results of this placebo-controlled trial were in accordance with previous studies. In VISUAL-I, a multicenter, double-masked controlled trial in patients with active non-infectious uveitis, adalimumab significantly reduced the risk of treatment failure by 50% compared to the placebo group.[19] In both VISUAL-I (active disease) and VISUAL-II (inactive disease), the risk to fail was halved and the time to fail was nearly doubled. A retrospective study in patients with refractory chronic uveitis demonstrated that adalimumab effectively controlled inflammation in 35% of patients refractory to previous treatment with infliximab or etanercept.[23] In a prospective open-label pilot study of 19 patients with various uveitic diagnoses, adalimumab significantly reduced inflammation in 63% of patients with complete resolution of cystoid macular edema (CME) in 55% affected eyes after 1 year of treatment.[24] In another non-comparative open-label prospective study of 31 patients with refractory uveitis, 68% of patients were clinical responders at 10 weeks, with sustained response at 50 weeks seen in 39% of the patients. [25] A multicenter prospective study of 131 patients with a mean age of 27 years also demonstrated that adalimumab therapy significantly improved anterior chamber and vitreous inflammation with the ability to taper CS.[14] The French uveitis network recently published a multicenter observational study of 160 patients with refractory uveitis treated with anti-TNFα (infliximab and adalimumab) agents. The patients had an overall response rate of 93% at 12 months.[26]

The low adalimumab immunogenicity observed in the current study was within the range of rates observed in other disease states.[13] The safety profile of adalimumab in this study was comparable

to other approved indications. The rate of AEs, serious AEs and discontinuation due to an AE were similar in both adalimumab and placebo groups.[13] No new safety signals were detected.[27,28] Previous clinical trials that were initiated to evaluate therapeutic potential for inactive, non-infectious uveitis have either failed to achieve their primary endpoint or were prematurely terminated due to unknown reasons.[29-31] Thus, VISUAL II is a first phase 3 trial of a nonsteroidal systemic medication in quiescent (inactive disease) patients to have reached its pre-specified primary endpoint (Time to treatment failure) and showed promise in treating inactive non-infectious uveitis in patients dependent on chronic oral CS (≥10 mg/d) to maintain disease inactivity.

The unique trial design, large study population, range of uveitis diagnoses and multiple component primary endpoint were strengths of this study. The composite primary endpoint assessed various facets of the disease, spanning from anterior to posterior segments of the eye, and facilitated detailed assessment of treatment response and efficacy since inflammation does not always manifest as a single endpoint such as VH. The CS-sparing effect of adalimumab could be assessed as all patients had a mandatory CS taper to zero.

There were limitations to the interpretation of the secondary endpoints (change in AC cell grade, VH grade, and visual acuity) as the magnitude of the treatment effect was diluted because only a small percentage of patients had treatment failure due to 1 of the 4 components. Thus, the magnitude of mean change observed was small for these secondary endpoints. There could have been a "floor effect", since most patients started with reasonably good visual acuity and minimal inflammation; it might have been difficult to detect a change particularly since more than half of the adalimumab group never achieved treatment failure. It is acknowledged that range of uveitis diagnoses, could also be recognised as a potential limitation since it does not provide us

information on which disease groups (with their recognised heterogeneity) are actually the responsive to the therapy. Due to difficulty in recruiting patients in a rare disease with multiple competing studies, no restriction on the number of recruiting sites was imposed, which we agree is a weakness of the study. In addition, the study was not statistically powered to analyze a differential efficacy among the different causes of uveitis.

Studies or clinical trials intended for the treatment of uveitis face number of challenges. Uveitis is a heterogeneous group of conditions characterized by intraocular inflammation. Most uveitis syndromes are individually rare, but for taxonomic and clinical convenience are commonly clustered according to their anatomical classification, despite the wide range of systemic and clinical associations they represent. Another challenge that is encountered in any uveitis trial is the lack of high quality outcome measure. Currently, VH grade, as defined by Nussenblatt, is a disease activity surrogate endpoint that is accepted by the FDA for clinical trials. This score utilizes a subjective ordinal scale of cloudiness of the vitreous humor, but has significant inter-observer variability.

Treatment with adalimumab significantly lowered the risk for uveitic flare or visual acuity loss in patients with steroid-dependent inactive, non-infectious intermediate, posterior, or panuveitis. No new safety signals were identified with adalimumab treatment; the safety profile of adalimumab was comparable to other approved indications. The findings from this study suggest that adalimumab may be well tolerated and offers an effective treatment option for patients with inactive, non-infectious uveitis and/or who are at risk of the long-term side effects of CS.

PANEL: RESEARCH IN CONTEXT Systematic Review: Evidence before this study

We searched PubMed for articles published up to March 20, 2016, in any language, for drugs/agents that have been used for the treatment of non-infectious uveitis and using the search terms: "non-infectious uveitis", "anti-TNF", "immunosuppression", and "biologics". There were numerous publications on the use of anti-TNF agents in the treatment of various types of anterior, intermediate, posterior or panuveitis. Several of these publications demonstrated the effectiveness of anti-TNF's (infliximab and adalimumab) in the treatment of uveitis. It is well known that some of the diseases for which adalimumab is currently indicated, such as JIA, AS and PsA, can present with uveitis. There have been reports of efficacy of adalimumab in pediatric patients with JIA-associated or idiopathic uveitis. A retrospective study in patients with refractory chronic uveitis demonstrated that adalimumab effectively controlled inflammation in 35% of patients refractory to previous treatment with infliximab or etanercept. In a prospective open-label pilot study of 19 patients with various uveitic diagnoses, adalimumab significantly reduced inflammation in 63% of patients with complete resolution of cystoid macular edema (CME) in 55% of eyes after 1 year of treatment. A multicenter study of 131 patients with a mean age of 27 years also demonstrated that adalimumab therapy significantly improved anterior chamber and vitreous inflammation with the ability to taper CS. In an open-label study of infliximab, 77% patients with refractory autoimmune uveitis achieved clinical success by week 10. In the open-label uncontrolled RHAPSODY study in AS patients, adalimumab decreased the rate of acute anterior uveitis flares by 51%. In a prospective study, adalimumab reduced anterior chamber and vitreous inflammation, improved visual acuity and reduced the corticosteroid burden in patients with refractory uveitis. The French uveitis network recently published a multicenter study of 160 patients with refractory uveitis treated with anti-TNFα (infliximab and adalimumab) agents. The patients had an overall response rate of 93% at 12

months. However, most of these are case reports/series or open-label studies. An adequate, well-controlled study of the efficacy and safety of anti-TNF therapy is lacking in the current literature. Previous clinical trials that were initiated to evaluate therapeutic potential for inactive, non-infectious uveitis have either failed to achieve their primary endpoint or were prematurely terminated due to unknown reasons.

Added value of this study

VISUAL-II is a multinational Phase 3, randomised, double-masked, study assessing the efficacy and safety of adalimumab in patients with inactive non-infectious intermediate, posterior, or panuveitis requiring corticosteroids. This study was done in 21 countries involving 62 study sites, representative of the global diversity of the study population. This is the first study to have achieved its pre-specified primary endpoint (Time to treatment failure) and showed promise in treating inactive non-infectious uveitis in patients dependent on chronic oral CS (≥10 mg/d) to maintain disease inactivity. The safety profile was consistent with the known safety profile of adalimumab across approved indications.

Interpretation: Implications of all the available evidence

Results from this study indicate that treatment with adalimumab significantly lowered the risk for uveitic flare or visual acuity loss in patients with steroid-dependent inactive, non-infectious intermediate, posterior, or panuveitis. No new safety signals were identified with adalimumab treatment; the safety profile of adalimumab was comparable to other approved indications. The findings from this study suggest that adalimumab may be well tolerated and offers an effective treatment option for patients with inactive, non-infectious uveitis and/or who are at risk of the long-term side effects of CS.

CONTRIBUTORS

Quan Dong Nguyen, Pauline T Merrill, Shree Kumar Kurup, John Sheppard, Ariel Schlaen, Carlos Pavesio, Luca Cimino, Joachim Van Calster and Andrew D Dick participated in the conduct of the study, including selection, treatment, and follow-up of patients; data interpretation; and preparation and critical review of the report. Quan Dong Nguyen, Glenn J Jaffe and Antoine P Brézin participated in the conception and study design; analysis and interpretation of data; and preparation and critical review of the report. Anne A Camez, Nisha V Kwatra, Alexandra P Song, Martina Kron, and Samir Tari participated in the analysis and interpretation of data; and preparation and critical review of the report. All authors provided a final review and approved the manuscript.

DECLARATION OF INTERESTS

Anne Camez, Martina Kron, Alexandra P Song, Nisha V Kwatra and Samir Tari are AbbVie employees and may hold AbbVie stock or options.

Quan Dong Nguyen has served on the Scientific Advisory Board for AbbVie, Santen, XOMA, Bausch & Lomb, Genentech uveitis studies, and chairs the Steering Committee for the VISUAL, EYEGUARD, and SAKURA studies.

Antoine P Brézin has served on advisory boards and as a consultant for AbbVie.

Glenn J Jaffe has served as a consultant for AbbVie.

Andrew D Dick has served on advisory boards for AbbVie.

Pauline T Merrill has served on the Steering Committee for the VISUAL studies and has served as consultant for Santen.

Shree Kumar Kurup has been an advisor and/or Steering Committee member for AbbVie, Allergan, Bayer, Clearside, Regeneron, and Xoma.

John Sheppard has been a consultant for AbbVie, Alcon, Allergan, Aldeyra, Bausch & Lomb, Clearside, EyeGate, Tear Lab, Tear Science, Santen; investigator for Xoma, Lux Biosciences, Eyegate, Alcon, Clearside, Alimera, pSivida, Aldeyra; steering committee for the VISUAL studies.

Luca Cimino has been on advisory boards and as a consultant for AbbVie.

Ariel Schlaen has no conflicts to declare.

Carlos Pavesio has received a research grant from Alcon and consultancy with Xoma, Servier and Santen, with advisory boards for all 3 plus Alcon and Bausch & Lomb.

Joachim Van Calster has served on advisory boards for AbbVie and MSD and has served as a consultant for MSD.

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Figure legends

Figure 1. Trial Profile

Figure 2. Treatment failure rate (Kaplan-Meier curve). (A) Treatment failure because of any reason, and **(B)** treatment failure rate due to vitreous haze, new lesions, anterior chamber cells, and best corrected visual acuity. HR=hazard ratio.

Figure 3. Causes of treatment failure. (A) Number of reasons for treatment failure per treatment group; **(B)** individual reasons for treatment failure per treatment group. Percentages of patients are indicated above the bars. TF=treatment failure.

Table 1. Patient Demographic and Baseline Characteristics (Intent-to-Treat Population)

	Placebo (n=111)	Adalimumab (n=115)
Sex, n (%)		
Female	72 (64·9)	66 (57·4)
Race, n (%)		
White	93 (83·8)	96 (83·5)
Black or African American	8 (7·2)	6 (5·2)
Asian	3 (2·7)	3 (2·6)
Other	5 (4·5)	9 (7·8)
Age, years		
Mean ± SD	42·2±14·0	42·9±12·9
Range	20-79	18-75
Type of Uveitis, n (%)		
Intermediate	30 (27·0)	17 (14·8)
Posterior	34 (30·6)	39 (33·9)
Panuveitis	46 (41·4)	57 (49·6)
Intermediate/Posterior	1 (0·9)	2 (1·7)
Diagnosis, n (%)		
Idiopathic	40 (36·0)	29 (25·2)
Birdshot Choroidopathy	15 (13·5)	15 (13·0)
Multifocal Choroiditis & panuveitis	2 (1·8)	5 (4·3)
Vogt Koyanagi Harada	25 (22·5)	26 (22·6)
Sarcoid	14 (12·6)	18 (15·7)

Behçet's	6 (5·4)	10 (8·7)
Other	9 (8·1)	12 (10·4)
Affected Eye, n (%)		
Left	3 (2·7)	2 (1·7)
Right	4 (3·6)	1 (0·9)
Both	104 (93·7)	112 (97·4)
Duration of Uveitis, months		
Mean ± SD	62·9±67·7	59·5±64·5
Range	4-394	2-381
No. of flares in past 12 months, n (%)		
0-1	46 (41·4)	48 (41·7)
2	40 (36·0)	43 (37·4)
≥3	25 (22·5)	24 (20·9)
Concomitant Immunomodulators at baseline, n (%)		
Azathioprine	11 (9·9)	3 (2·6)
Cyclosporine	11 (9·9)	15 (13·0)
Methotrexate	14 (12·6)	19 (16·5)
Mycophenolate mofetil	17 (15·3)	17 (14·8)
Tacrolimus	0	0

Table 2. Summary of Ranked Secondary Efficacy Variables (ITT population)

Ranked Secondary Variable*	Placebo (n=111)		Adalimumab (n=115)		*P*
	n[a]	Mean	n[a]	Mean	Value
1. Change in AC cell grade					
Left eye	110	0·57	115	0·41	
Right eye	110	0·53	115	0·40	
Difference, mean (95% CI)		-0·14 (-0·37, 0·08)			0·218[b]
2. Change in VH					
Left eye	110	0·33	115	0·16	
Right eye	110	0·27	115	0·18	
Difference, mean (95% CI)		-0·13 (-0·28, 0·01)			0·070[b]
3. Change in logMAR BCVA					
Left eye	110	0·06	115	0·01	
Right eye	110	0·02	115	-0·01	
Difference, mean (95% CI)		-0·04 (-0·08, 0·01)			0·096[b]
4. Time to OCT evidence of ME (months) on or after Week 2	95	NE	90	NE	
Median					
Hazard ratio (95% CI)		0·75 (0·34, 1·69)[c]			0·491[f]
5. Percent change in central retinal thickness					
Left eye	107	6·4	114	4·5	

Right eye	108	7·7	113	5·4	
Difference, mean (95% CI)		-2·3 (-8·5, 3·8)			0·451[d]
6. Change in VFQ-25 total score	109	1·24	115	3·36	
Difference, mean (95% CI)		2·12 (-0·84, 5·08)			0·16[e]
7. Change in VFQ-25 distance vision subscore	109	0·76	115	2·64	
Difference, mean (95% CI)		1·88 (-2·53, 6·29)			0·40[e]
8. Change in VFQ-25 near vision subscore	109	3·98	115	3·88	
Difference, mean (95% CI)		-0·10 (-4·81, 4·61)			0·97[e]
9. Change in VFQ-25 ocular pain subscore	109	2·87	115	3·42	
Difference, mean (95% CI)		0·56 (-4·56, 5·68)			0·83[e]

AC=anterior chamber; BCVA=best-corrected visual acuity; ME=macular edema; OCT=optical coherence tomography; VFQ-25=Visual Functioning Questionnaire-25; VH=vitreous haze.

*With the exception of endpoint 4 (time to OCT evidence of ME), data reflect change from BL to final or early termination visit

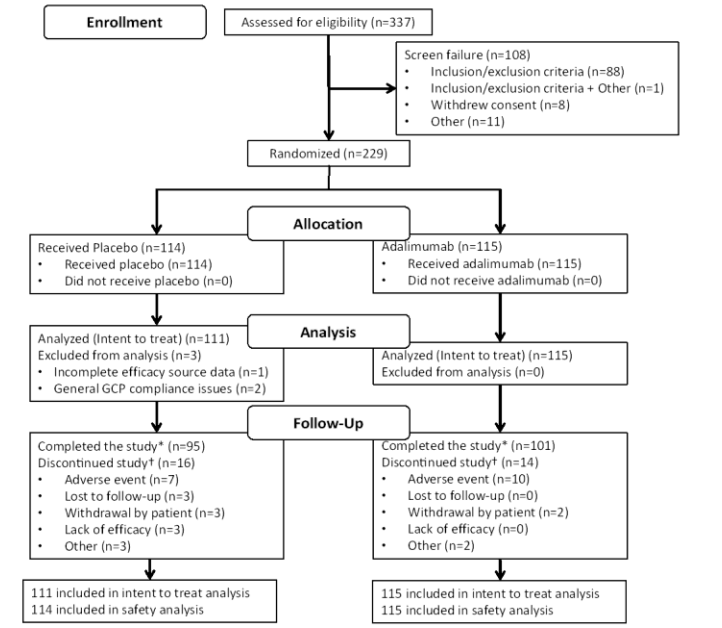
a. For each endpoint, n = number of patients with non-missing value.
b. From ANOVA of change from BL to the final/early termination visit with treatment as factor adjusted for clustered observations.
c. HR of adalimumab vs placebo from proportional hazards regression with treatment as factor.
d. From ANOVA of change from BL to the final/early termination visit with treatment and type of OCT machine as factors adjusted for clustered observations
e. From ANOVA of change from BL to the final/early termination visit with treatment as factor.
f. Log rank test.

Table 3. Adverse Events (Safety Population)

AEs, Events (Events per 100PY)	Placebo (N=114, PYs=71·0)	Adalimumab (N=115, PYs=94·5)
Any AE	642 (905)	831 (879)
AE leading to death*	0	2 (2·1)
Serious AE	10 (14·1)	13 (13·8)
AE leading to discontinuation of adalimumab/placebo	7 (9·9)	11 (11·6)
Serious infectious AE	2 (2·8)	3 (3·2)
Injection site reactions	16 (22·6)	36 (38·1)
Malignancies†	0	1 (1·1)
Opportunistic infections (excluding oral candidiasis and TB)	0	0
Active tuberculosis	0	0
Latent tuberculosis	1 (1·4)	3 (3·2)
Demyelinating disease	0	0
Lupus-like reaction	0	0
Allergic reactions (including angioedema, anaphylaxis)	8 (11·3)	5 (5·3)

*One death, due to2 fatal AEs of aortic dissection and cardiac tamponade (18 days after last ADA dose), not related to ADA treatment. †One event of non-serious squamous cell carcinoma of skin (day 210; resolved on day 215; ADA treatment was not interrupted).

Figure 1.



*Includes patients who experienced treatment failure or reached 80 weeks of treatment without treatment failure. †Some patients had multiple reasons for discontinuation; total counts for reasons for discontinuation exceed the total number of discontinuations.

Figure 2.

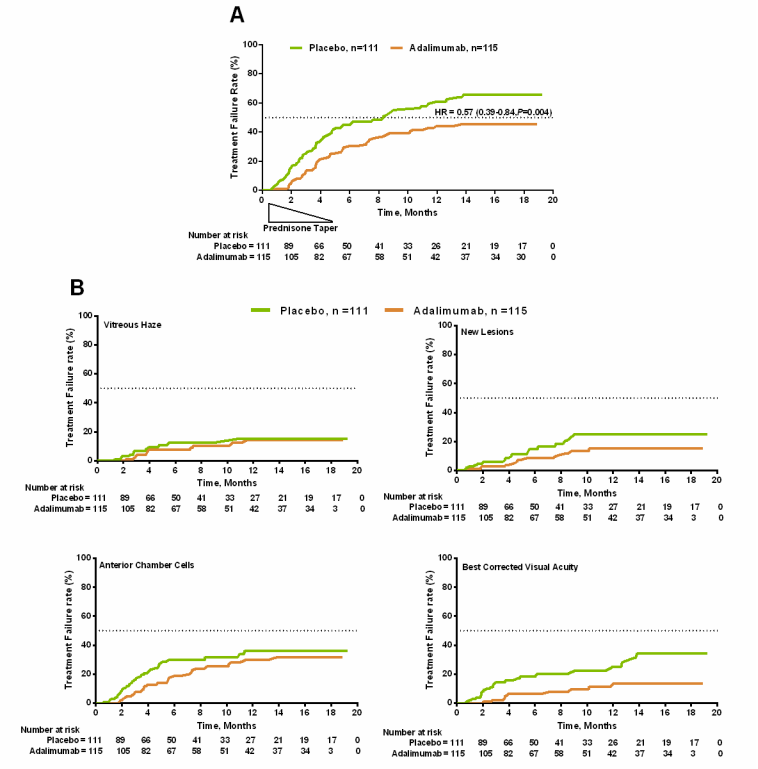
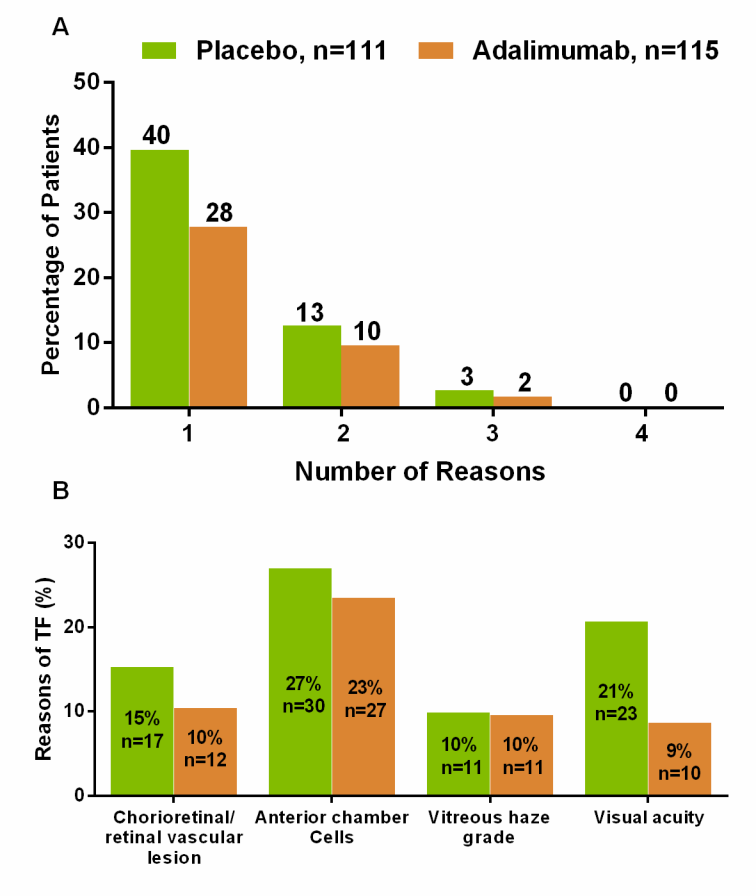


Figure 3.


A
Placebo, n=111
Adalimumab, n=115
Percentage of Patients
50
40
30
20
10
0
40
28
13
10
3
2
0
0
1
2
3
4
Number of Reasons
B
Reasons of TF (%)
30
20
10
0
15% n=17
10% n=12
27% n=30
23% n=27
10% n=11
10% n=11
21% n=23
9% n=10
Chorioretinal/ retinal vascular lesion
Anterior chamber Cells
Vitreous haze grade
Visual acuity